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Review

# Autoimmune aspects of psoriasis: Heritability and autoantigens☆,☆☆

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ABSTRACT

Chronic immune-mediated disorders (IMDs) constitute a major health burden. Understanding IMD pathogenesis is facing two major constraints: Missing heritability explaining familial clustering, and missing autoantigens. Pinpointing IMD risk genes and autoimmune targets, however, is of fundamental importance for developing novel causal therapies. The strongest association of all IMDs is seen with human leukocyte antigen (HLA) alleles. Using psoriasis as an IMD model this article reviews the pathogenic role HLA molecules may have within the polygenic predisposition of IMDs. It concludes that disease-associated HLA alleles account for both missing heritability and autoimmune mechanisms by facilitating tissue-specific autoimmune responses through autoantigen presentation.



**Contents**



## 1. Introduction

Chronic, immune-mediated diseases (IMDs) represent a heterogeneous group of multifactorial disorders [1–3]. It comprises ankylosing spondylarthritis, rheumatoid arthritis, Crohn's disease, ulcerative colitis,

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psoriasis vulgaris, type I diabetes mellitus (T1D), multiple sclerosis (MS), systemic lupus erythematodes, Behçet's disease, and many others [3,4]. IMDs constitute the third-greatest burden for clinical treatment, after cardiovascular diseases and cancer [5]. In IMDs the combined effects of a polygenetic predisposition and environmental influences eventually induce chronic and self-perpetuating inflammation that result in damage to organs, tissues, or cells. While much of the knowledge about immunological disorders is based on murine disease models, the pathomechanisms of human IMDs are still incompletely resolved. The strongest genetic association is seen with certain HLA alleles but the role of the HLA polymorphisms in disease pathogenesis has remained mysterious, because the extensive linkage disequilibrium within the major histocompatibility complex (MHC) did not allow for a precise risk allocation to a particular gene. Although being viewed as autoimmune or autoimmune-related in nature, final evidence of the autoimmune character of most IMDs is missing because precise target cells or autoantigens of the suspected autoimmune responses are still unknown. Accordingly, it has remained largely elusive how genetic traits cooperate with innate and adaptive immune mechanisms in driving IMD manifestation [4,6,7]. Recent insights into the pathomechanisms of psoriasis now provide evidence that the disease-associated HLA alleles represent the key for resolving both missing heritability and missing autoantigens. This allows for redefining the pathogenetic concepts of HLA-associated IMDs.

## 2. IMDs: missing heritability

### 2.1. Familial clustering and genome-wide association studies

Familial clustering and the concordance rate in monozygotic twins indicate that IMDs have a heritable etiology. Unlike rare monogenic autoimmune disease syndromes with highly penetrant mutations, however, IMDs are multifactorial [8–10]. They involve the interaction of individual genotypes with environmental, infectious and lifestyle factors [11]. Initially, identification of disease risk genes was based on candidate gene analyses and family-based linkage studies [12]. Completion of the Human Genome Project and International HapMap Project and the introduction of array based approaches then facilitated a hypothesis-free survey of the human genome for gene variants associated with disease susceptibility [12–15]. For each IMD, genome-wide association studies (GWAS) revealed a complex genetic predisposition and identified numerous disease-associated gene loci [12,13,16]. The Major Histocompatibility Complex (MHC) region on human chromosome 6, which harbours the HLA alleles, stands out as the most prominent susceptibility locus for all IMDs [12,17]. Outside the MHC region, GWAS revealed mainly common gene variants which exert only modest individual effects, explain only a small proportion of familial disease clustering and ostensibly act independently [18]. Only for a few association signals has the causal gene been identified, and for even fewer have the causal variant and underlying mechanism been defined. While some of the susceptibility loci outside the MHC appear to be disease- or phenotype-specific, many others are shared across IMDs and implicate similar susceptibility pathways in multiple diseases [12,13,19–22]. For particular IMDs 70 or more non-HLA risk loci were identified. They result in small increments with additive effects for disease risk but overall still explain only a minor proportion of the familial inheritance. Together the allelic variants usually make up for 20% to 50% of heritability [23]. Thus, despite compelling genetic insights, much of the genetic contribution to complex traits remains unresolved. Proposed explanations for the missing heritability include that the effect size of common gene variants may be too small to be detected in cohorts with limited sample size, or that rare disease alleles are not covered by GWAS. Furthermore, non-additive epistatic gene-gene interactions might generate greater-than expected risk effects [13,24]. Polygenic disorders are therefore mainly interpreted as quantitative traits where the additive effects of hundreds of risk loci with moderate risk size account for a substantial part of inheritance [25–27]. Because the identified associations are neither necessary nor sufficient for causing disease, and patient populations in any disease are inevitably heterogeneous [19,28,29] it has been doubted, if single genes explaining a large proportion of heritability for complex diseases exist at all [24].

### 2.2. HLA-association: the strongest genetic signal in IMDs

This conclusion turns the attention back to the HLA association of IMDs. Few, if any genetic signals of IMDs are stronger than the associations with the human MHC [13,30]. This reflects the HLA association of IMDs that has been known for more than 4 decades: Virtually all autoimmune conditions are found in association with particular HLA-class I or class II alleles or both if large enough cohorts are being studied [17,31–33]. The HLA alleles are localized in the MHC on chromosome 6p21. They are extremely polymorphic. By 2017 there are more than 16.000 HLA and related alleles described by the HLA nomenclature, comprising more than 12,000 HLA-class I alleles and 4200 HLA-class II alleles (IPD-IMGT/HLA Database). In view of this exceptionally high diversity it is particularly remarkable that only select HLA alleles are linked with autoimmune diseases: While IMDs share many of the non-HLA loci, the associated HLA class I and/or class II alleles are usually disease-specific [34]. This pleads for a direct causal role in IMD pathogenesis.

The density of genes and the strong linkage disequilibrium within the MHC as well as the lacking functional implementation of disease-associated HLA alleles have hitherto thwarted an identification of the precise role of particular HLA molecules in IMD susceptibility. Only few experimental reports have assigned particular HLA-molecules with a direct role in disease pathogenesis. Transgenic expression of HLA-DRB1*1501, the main MS risk allele, caused a T-cell mediated MS-like disease in mice [35]. Humanized mice expressing another MS risk allele, HLA-A*03:01, and an HLA-A*03:01-restricted myelin proteolipid protein-specific T-cell receptor (TCR) isolated from MS patients developed a disease resembling human MS [36,37]. Occurrence of arthritis in rats or mice transgenic for *HLA-B27:05*, the main risk allele for ankylosing spondylitis, indicated that the encoded HLA proteins and not genes in linkage disequilibrium with *HLA-B27* are responsible for joint inflammation [38–40]. Because HLA-B27 molecules present peptides from cytoplasmic proteins on the cell surface [41,42] and act as restriction elements for $CD8^+$ T-cell responses [43,44] it was proposed that HLA-B27 may induce autoimmune responses through presentation of arthritogenic self-peptides. Aberrant cell-surface expression of HLA-B27 heavy chain homodimers or HLA-B27 misfolding inside the endoplasmic reticulum were considered as alternative causes for innate immune dysregulation [45,46]. Yet, despite these intense investigations the pathogenic mechanisms by which HLA alleles cause disease remained elusive.

## 3. Challenges from HLA antigen presentation and TCR antigen recognition

### 3.1. HLA antigen presentation and autoimmune responses

The natural immunological function of HLA molecules is presentation of peptide antigens to the TCRs for cognate antigen recognition by T cells [47,48]. HLA polymorphisms mostly refer to pockets of the peptide binding groove which determines the peptide repertoires by specific acceptor sites or pockets that bind side chains of particular amino acids localized at certain positions within the peptide. The peptide residues in between the anchor amino acids may be flexibly occupied. A single HLA molecule can theoretically display between $6 \times 20^{5-7}$ (HLA class I) and $12 \times 20^{10}$ (HLA class II) different peptides [47,49,50]. Different HLA molecules select different peptide repertoires for presentation [51,52], although the binding specificities may overlap [53,54]. Accordingly, induction of T-cell mediated autoimmune responses through

presentation of self-peptides by select HLA molecules would be the most straightforward explanation for the HLA association of IMDs [55].

HLA-class I- and II-molecules differ regarding their expression patterns and the origin and length of the peptide antigens they present. This should have essential consequences for potential autoimmune responses. HLA-class I molecules are expressed on all nucleated cells. They present peptide antigens of usually 8–10 amino acid lengths to αβ TCRs of $CD8^+$ T cells [56]. The peptides are derived from intracellular, i.e. cytoplasmic proteins generated within cells that were degraded by the proteasome, translocated into the endoplasmic reticulum and subjected to N-terminal trimming by the endoplasmic reticulum peptidases 1 and 2 (ERAP1/2) [56–58]. This reflects the primary role of HLA-class I-molecules to present antigens from viruses that replicate intracellularly within infected cells and otherwise would escape immune recognition [47]. Consequently, an HLA-class I-restricted autoimmune response by $CD8^+$ T cells should be directed against a particular target cell expressing the protein which is the source of the autoantigenic peptide [57,58]. Expression of HLA-class II molecules is mostly restricted to professional antigen-presenting cells including macrophages, dendritic cells and B cells [57]. HLA-class II-molecules screen the environment for antigenic danger signals. The antigenic peptides are primarily derived from extracellular proteins degraded in the endocytic pathway. They have a 9-amino acid core but the peptides vary greatly in length, because the flanking residues may extend out of the HLA-class II-binding groove and [59]. HLA-class II-antigen presentation activates $CD4^+$ T cells which promote inflammation and antibody formation. Hence, HLA-class II-associated autoimmune diseases are usually characterized by formation of autoantibodies [60]. Unlike HLA-class I-presented cytoplasmic antigens, which should be derived from the proteome of a particular cell, neither source nor length of autoantigens for $CD4^+$ T cells can be anticipated.

### 3.2. TCR antigen recognition and polyspecificity

The TCRs of pathogenic T cells hold the clue to defining the role of HLA alleles in autoimmune diseases. They determine both HLA-restriction and antigen specificity and thus define the precise reactivity of adaptive immune responses. A T-cell mediated immune response begins with the formation of a trimolecular complex between the TCR of a T cell and a peptide presented by the appropriate HLA molecule. Upon antigen recognition, T cells become activated and undergo clonal expansion at the site of antigen exposure. Due to TCR diversity, any two T cells expressing the same TCR likely arose from a common progenitor T cell [7]. TCR clonotypes designate the T cells involved in pathogenic circumstances that have expanded in response to local antigen stimulation [7,61]. Clonal T-cell expansions characterize inflammatory infiltrates of IMDs such as MS, ankylosing spondylitis, coeliac disease, Crohn's disease, rheumatoid arthritis, and type I diabetes mellitus [62–72]. The TCR clonotypes from tissue infiltrates can be used for analysing HLA restriction and antigen specificity of pathogenic T-cell responses. As several aspects limit the availability and experimental use of pathogenic T cells in human diseases, such approaches currently rely mainly on cloned TCRs [7]. This requires identification and isolation of the clonally expanded pathogenic T cells from complex inflammatory infiltrates and analysis of their TCR rearrangements.

Conventional T cells express unique αβ TCRs composed of an α- and β-chain, each generated by somatic recombination of diverse V(D)J gene segments and random addition or deletion of nucleotides at the recombination sites [73]. The comparatively small size of the human TCR repertoire of an estimated $10^7$ to $10^8$ different αβ TCRs [61], which faces the huge peptide antigen diversity presented by HLA molecules, is compensated by the fact that TCRs are polyspecific [49,50,74–76]. A single TCR can recognizes more than one million distinct decamer peptides in the context of a single HLA-class I molecule once they share amino acid anchor and TCR contact residues defining them as TCR ligands [77]. While this principle guarantees the recognition of a broad antigen spectrum it creates a major challenge for antigen identification: the precise peptide antigen of a pathogenic autoimmune response has to be unequivocally identified from the universe of potential TCR ligands [76,77]. In this context HLA-class I-associated IMDs may offer advantages over HLA-class II-risk genes. The origin of HLA-class I-presented molecules from cytoplasmic proteins limits the spectrum of potential autoantigens to the target cell proteome. This makes the identification of the target cells of HLA-class I-restricted autoimmune responses an essential precondition. The first HLA-class I-associated IMD, in which resolving this experimental challenge successfully determined the role of the main HLA risk gene, defined the autoimmune target cell type and identified an autoantigen by using a pathogenic TCR, is psoriasis vulgaris [78].

## 4. HLA-C*06:02 and T-cell responses in psoriasis

### 4.1. HLA-C*06:02 and $CD8^+$ T cells in psoriasis

Psoriasis vulgaris [MIM177900] is a common inflammatory skin disease characterized by T-cell driven epidermal hyperplasia. T cells infiltrating psoriasis skin lesions display a T-helper/cytotoxic cell ($T_{h/c}$) 17 phenotype and drive psoriatic inflammation through a complex cytokine pattern with the signature cytokines interleukin (IL)-17A, IL-22 and IFN-γ [79,80]. Psoriasis is multifactorial and has a complex genetic predisposition. *HLA-C*06:02* is the major psoriasis risk gene in Caucasian populations [81–83]. It is located in the psoriasis susceptibility locus 1 within the MHC on chromosome 6 (*PSORS1* on 6p21.3), which accounts for approximately 50% of disease risk [84–86]. Other psoriasis associated HLA variants with lesser Odds ratios are HLA-C*07:04, HLA-C*12:03, HLA-B*27, HLA-B*57, HLA-B amino acid positions 67 and 116, HLA-A amino acid position 95, and HLA-DQA1 amino acid position 53, and others [82,87,88]. Psoriasis heritability explained by GWAS variants outside the MHC was estimated at about 20% [89], while the remaining 30% of disease risk are attributed to environmental factors [90]. *HLA-C*06:02* defines familial clustering, early onset and a more severe course of psoriasis [91–93]. Accordingly, *HLA-C*06:02* is a paradigmatic HLA-risk gene.

The *HLA-C*06:02* association of psoriasis would be consonant with the presentation of self-antigens to pathogenic $CD8^+$ T cells. Indeed, $CD8^+$ T cells play a prominent role in psoriasis. The formation of psoriasis lesions depends on the epidermal influx, activation and clonal expansion of $CD8^+$ T cells, which predominate the epidermal infiltrate and preferentially rearrange Vβ3 or VB13S1 TCR genes [94–98]. Together with the persistence or reappearance of the same clonal T cells in chronic or relapsing psoriasis lesions [99,100] and sharing of lesional TCRs between monozygotic twins concordant for psoriasis [101] these findings emphasize that dominant tissue autoantigens drive lesional psoriatic T-cell activation and inflammation. Accordingly, understanding the immunopathogenesis of psoriasis demanded answers to two fundamental but tightly linked issues: What is the role of the main psoriasis risk gene, *HLA-C*06:02*, and which are the antigens of the lesional psoriatic $CD8^+$ T-cell response?

### 4.2. Use of a TCR hybridoma to identify the target cells of the psoriatic autoimmune response

We had addressed these two issues by the use of a paradigmatic pathogenic psoriatic Vα3S1/Vβ13S1 TCR. It had been obtained by single-cell TCR analysis from a pervasive epidermal $CD8^+$ T-cell clone identified in the lesional infiltrate of an HLA-C*06:02-positive psoriasis patient [95]. The Vα3S1/Vβ13S1 TCR was expressed as recombinant TCRs along with human CD8 α and β chains in an NFAT-sGFP T-hybridoma cell line that reports on TCR signalling by robust sGFP expression [102,103]. Consequently, this functional TCR hybridoma carried the specificity of the lesional psoriatic T-cell response. The reactivity of the Vα3S1/Vβ13S1 TCR was characterized in a two-armed strategy: arm I

determined HLA-restriction and target cell type, while arm II recovered artificial peptide ligands of the Vα3S1/Vβ13S1 TCR from combinatorial peptide libraries, determined the conserved amino acid pattern of Vα3S1/Vβ13S1-TCR ligands and searched for corresponding peptide epitopes in the proteome of the target cells. We then combined the results from both arms and tested the antigenicity of candidate peptide antigens identified in arm II in the context of the full-length parent proteins within the target cell type identified in arm I [78].

These experiments revealed that the Vα3S1/Vβ13S1-TCR reacted specifically against melanocytes or melanoma-derived melanocytic cell lines in an HLA-C*06:02-restricted manner. High frequencies of $CD8^+$ T cells in direct contact with melanocytes in psoriasis skin lesions indicated that the Vα3S1/Vβ13S1-TCR reactivity is representative of the lesional psoriatic T-cell response in general. These $CD8^+$ T cells polarized granzyme B-containing granules towards the melanocyte contact sites indicating TCR-mediated activation without signs of cytotoxicity [78,104]. Hence, the unbiased analysis of the lesional psoriatic Vα3S1/Vβ13S1 TCR had allowed for two fundamental novel insights into psoriasis pathogenesis: the protein encoded by *HLA-C*06:02*, the main psoriasis risk gene, mediates an autoimmune response against melanocytes as target cells of the lesional psoriatic $CD8^+$ T-cell response.

### *4.3. HLA-class I-presented autoantigens are determined by antigen processing*

Identification of melanocytes as specific target cells of the HLA-C*06:02-restricted autoimmune T-cell response in psoriasis provided the key for identification of the causative autoantigen from various antigen candidates. After having determined the conserved amino acid pattern of peptide ligands recognized by the Vα3S1/Vβ13S1-TCR in the context of HLA-C*06:02 we searched the transcriptome of melanocytes and the human proteome for proteins containing corresponding peptides. Of approximately 200 self-peptide candidates tested, peptides from six human proteins stimulated the Vα3S1/Vβ13S1-TCR hybridoma when presented by HLA-C*06:02. In the context of the full-length parent proteins however, only a peptide epitope from ADAMTS-like protein 5 (ADAMTSL5) kept its antigenicity for the Vα3S1/Vβ13S1 TCR, and this property depended on expression of the ADAMTSL5-parent protein in melanocytes as psoriatic target cells, but not in other cell types.

These data document that the human proteome may contain many peptide antigens that can be recognized by an autoreactive TCR. The actual immunogenicity of self-peptides, however, is limited by antigen-processing and may be cell-type specific. For presentation under natural conditions antigenic peptides need to be generated from the full-length parent protein by proteasomal degradation [58,105]. This involves preferred proteasomal cleavage sites and cell-type dependent differences in antigen processing and limits the spectrum of potentially autoantigenic self-peptides to select proteins and tissues or cell types [58,106,107]. Accordingly, for final validation of HLA-class I-presented candidate peptide autoantigens the antigenicity of the full-length protein has to be verified within the target cell. Only this approach may finally confirm that a TCR peptide ligand from a natural protein is an actual autoantigen.

## 5. Autoimmune disease criteria in psoriasis

In 1993 N. R. Rose and C. Bona had revisited the criteria for establishing the autoimmune etiology of a human disease [108]. In psoriasis, HLA association [81,83], oligoclonal lymphocytic infiltration of the target organ and restricted TCR Vβ-gene usage [96,98] as well as the favourable response to immunosuppression [109] represent circumstantial evidence. Indirect evidence for an autoimmune pathogenesis results from triggering psoriasis onset through checkpoint inhibition [110,111] which may induce various autoimmune-related adverse drug reactions [112], and from the adoptive transfer or resolution of psoriasis by bone marrow or autologous stem cell transplantation [113–116]. The findings from the unbiased analysis of a pathogenic psoriatic TCR now define an HLA-restricted autoimmune response as a central and disease-specific event in psoriasis pathogenesis. They show that the HLA molecule, which is encoded by the main psoriasis risk gene, *HLA-C*06:02*, mediates an autoimmune response against melanocytes through autoantigen presentation. The identification of melanocytes as organ-specific autoimmune target cells and of ADAMTSL5 as a melanocytic autoantigen provides direct experimental evidence for the autoimmune nature of psoriatic inflammation. Because melanocytes are a selectively skin-resident cell population and account for 5–10% of all epidermal cells [117] this also explains why psoriasis primarily targets the skin.

## 6. Correlating GWAS results and immune pathomechanisms in psoriasis

Defining the functional role of *HLA-C*06:02* in psoriasis may now help to understand how gene variants identified by GWAS may affect autoimmune disease manifestation and allow for re-defining the architecture of the pathogenic immune response. GWAS and more targeted candidate gene approaches have identified more than 40 psoriasis-associated SNPs at a genome wide significance level [89,118–129]. Except for the MHC locus they mostly represent common genetic variants with low effect size. They can be grouped into genes affecting innate immune pathways, antigen presentation, activation and differentiation of $CD8^+$ T cells and the IL-23/IL-17 axis (Table 1). Overall, they reflect the different stages of the innate and adaptive immune activation cascade for mounting the $CD8^+$ T-cell response in psoriasis. The following paragraph briefly summarizes the function of these gene variants and how they might impact on the psoriatic autoimmune response. The precise effects of most GWAS risk loci on biological pathways however, are still not sufficiently clarified and their role remains largely hypothetical. Because the GWAS results have been extensively discussed in various reviews [130–135] only specific aspects related to the focus of this manuscript are addressed here.

### *6.1. Gene loci related to innate immunity*

Initiation, magnitude and quality of adaptive immune responses require proinflammatory signals from the innate immune system [136]. Various psoriatic risk loci point to an increased responsiveness of innate immunity to trivial or unspecific triggers, which may enhance type-I interferon and NF-κB signalling pathways and hereby promote the initiation of T-cell responses.

IFN-α is a strong activator of adaptive immunity [137]. The initial phase of psoriasis involves the production of IFN-α by plasmacytoid dendritic cells [138]. Various candidate gene loci related to type I interferon induction and signalling are associated with psoriasis risk (Table 1). *ELMO1* encodes the engulfment and cell motility protein 1 which interacts with DOCK2 and is essential for Toll-like receptor-induced IFN-α

**Table 1**
Major non-MHC psoriasis GWAS loci in European and Chinese populations [89,118–129].

| | Affected pathways | Genes/loci |
|---|---|---|
| Innate immunity | IFN signalling | *ELMO1*, *TYK2*, *SOCS1*, *IFIH1/MDA5*, *RNF114*, *IRF4*, *RIG1/DDX58*, *IFNLR1/IL28RA*, *IFNGR2* |
| | NFκB signalling | *TNFAIP3*, *TNIP1*, *TYK2*, *REL*, *NFkBIA*, *CARD14*, *CARM1*, *UBE2L3*, *FBXL19* |
| Acquired immunity | Antigen presentation | *ERAP1* |
| | $CD8^+$ T-cell maturation, activation and differentiation | *ETS1*, *RUNX3*, *TNFRSF9*, *MBD2*, *IRF4* |
| | $T_{h/c}17$-differentiation, IL-23 and IL-17 signalling pathways | *IL23R*, *IL12B*, *IL12RB*, *IL23A*, *IL23R*, *TYK2*, *STAT3*, *STAT5A/B*, *SOCS1*, *ETS1*, *TRAF3IP2*, *KLF4*, *IF3* |

induction in plasmacytoid dendritic cells [139,140]. Suppressor of cytokine signalling, SOCS1, reduces IFN responses through inhibition of Tyrosine kinase 2 (Tyk2)-mediated STAT signalling and negatively impacts IFN-α receptor 1 surface expression [141]. The ubiquitin binding protein RNF114 regulates a positive feedback loop that enhances production of type I IFN induced by cytoplasmic double-stranded RNA (dsRNA) [142]. DNA sensing by plasmacytoid dendritic cells through LL37 and endosomal Toll-like receptors is a potent trigger of interferon production in psoriasis [143]. Proteins encoded by two psoriasis-associated variants, *IFIH1*-encoded MDA5 (melanoma differentiation-associated gene 5) and its paralog retinoic acid-inducible protein 1 (RIG1/DDX58) are cytoplasmic nucleic acid-sensing receptors which coordinate with each other to evoke downstream signalling events that promote robust type I-IFN responses and NF-κB activation [144,145].

NF-κB is a key transcription factor in immune responses. NF-κB activity is inducible in all cell types and regulates transcription of many genes which encode cytokines and other proinflammatory mediators. NF-κB is activated by TNF-α and other members of the TNF-α family [146]. TNF-α blockade is highly effective in psoriasis treatment and other IMDs [147]. Hyperactivation of NF-κB in skin induces a T-cell dependent psoriatic phenotype in a mouse model of inflammation [148]. Various gene variants of the NF-κB pathway contribute to psoriasis risk (Table 1). *TYK2*, *REL* and *CARM1* encode proteins essential for NF-κB activation and signalling [119,149,150]. Proteins encoded by *NFKBIA*, *FBXL19*, *UBE2L3*, *TNIP* and *TNFAIP3* have inhibitory effects on NF-κB activation [151–155]. The best characterized variants represent gain of function mutations in *CARD14*. *CARD14* encodes Caspase recruitment domain-containing protein 14 that activates NF-κB. It is the causative gene at PSORS2 [156,157]. CARD14 is mainly expressed in keratinocytes and dermal endothelial cells [156,158]. Psoriasis-associated gain-of-function mutations in *CARD14* lead to unopposed NF-κB activation and transcription of inflammatory mediators in keratinocytes in response to proinflammatory triggers or physical injury [156]. The association with psoriasis but also another inflammatory skin disease, Pityriasis rubra pilaris [159], indicates that *CARD14* mutations exert an organ-selective proinflammatory effect which may precipitate epidermal immune reactions.

### 6.2. Gene loci related to antigen presentation

All major HLA-class I-associated disorders including ankylosing spondylitis [160], MS [161], T1D [162] and Behçet's disease [163] show associations with distinct variants of *ERAP1*, a gene encoding the endoplasmic reticulum aminopeptidase 1. ERAP1 governs the final step of peptide antigen generation by N-terminal trimming of antigenic precursors to the length appropriate for binding to HLA-class I molecules. Different *ERAP1* variants show different cleavage activities and fine substrate preferences and hence may influence the antigenic peptide repertoire [164–167]. *HLA-C*06:02* in psoriasis is found in epistasis with certain *ERAP1* variants [126,168]. A variant protective for psoriasis reduced the antigenicity of the ADAMTSL5 peptide and melanocytes (unpublished result). This verifies for a defined autoantigen how the genetic interaction between an HLA-class I allele and *ERAP1* variants may affect disease risk through peptide destruction.

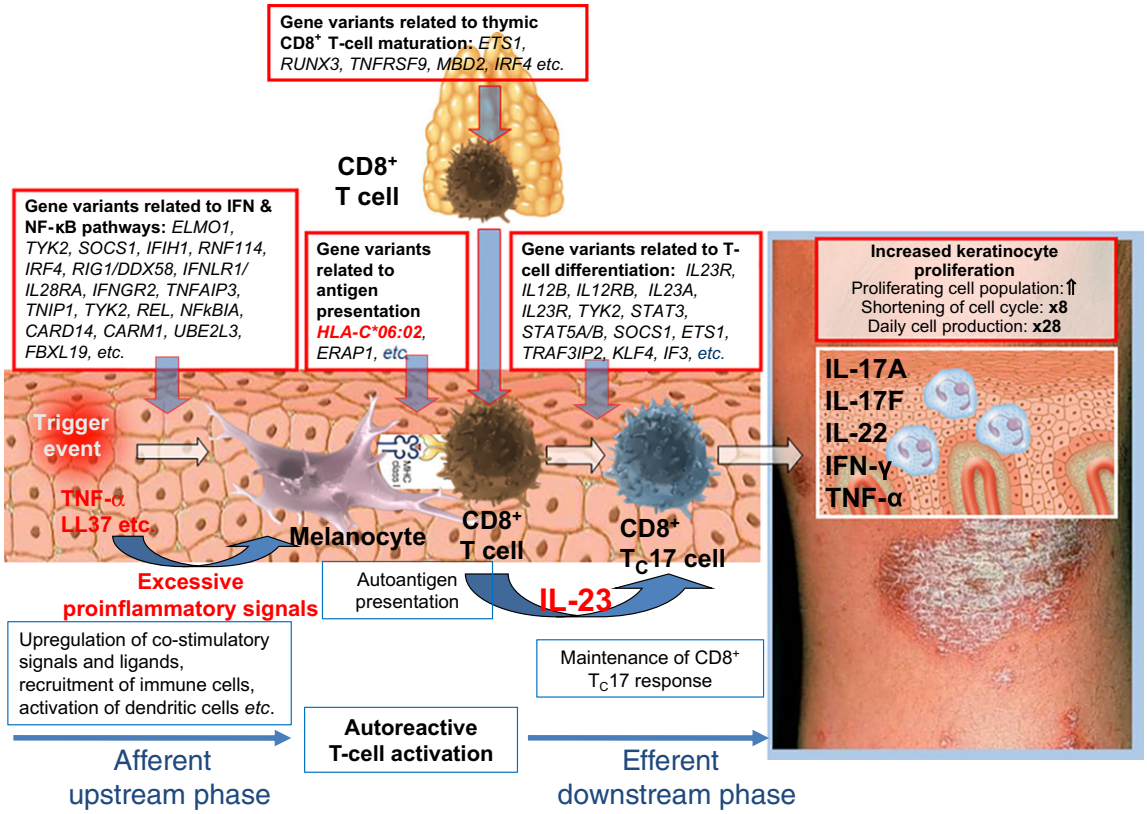


**Fig. 1.** Model of psoriasis pathogenesis. Select HLA-molecules, in particular HLA-C*06:02, predispose for an autoimmune response against melanocytes through presentation of autoantigenic peptides, which are generated in melanocytes from cytoplasmic proteins and trimmed to the appropriate size by certain ERAP1 variants. The complex of peptide and HLA-class I molecules is recognized by $CD8^+$ T cells, which have been conditioned for an increased responsiveness during thymic T-cell development under the influence of gene variants related to $CD8^+$ T cell differentiation. In the afferent upstream phase of the melanocyte-specific autoimmune response gene variants related to increased IFN-α signalling and NF-κB activation induce an increased inflammatory response which recruits various immune cells and provides the secondary signals for autoreactive T-cell activation upon unspecific proinflammatory triggers. In the efferent downstream phase of the autoimmune response gene variants related to the IL-23/IL-17A axis maintain $CD8^+$ T cell differentiation into a $T_c17$ phenotype which promotes psoriatic inflammation through the psoriasis signature cytokines IL-17A, IL-17F, IFN-γ and TNF-α and enhanced IL-17A signalling.

### 6.3. Gene loci affecting activation and differentiation of $CD8^+$ T cells

Epidermal infiltration, activation and expansion of $CD8^+$ T cells are key events in psoriasis onset. Various psoriasis risk loci involve genes related to the generation and differentiation of $CD8^+$ T cells (Table 1). The transcription factor ETS1 enhances expression of RUNX3. RUNX3 cooperates with ETS1 in regulating the development of $CD8^+$ T cells by repressing CD4 expression and initiating cytotoxic gene expression during the differentiation of MHC-class I-restricted thymocytes [169–172]. *TNFRSF9* (alternative nomenclature CD137, 4-1BB, ILA) is a member of the TNF receptor family. It is primarily expressed on activated T cells and promotes the expansion and memory formation of $CD8^+$ T cells [173,174]. Methyl-CpG-binding domain protein 2, MBD2, is involved in the efficient generation of memory effector cells from naïve $CD8^+$ T cells [175]. Interferon regulatory factor 4 (IRF4) is vital for the expansion and effector differentiation of $CD8^+$ T cells [176].

### 6.4. Gene loci related to IL23/T17 pathways

The IL-23/T17 axis has a sentinel role in psoriasis [177]. Blocking IL-23 or IL-17 has strong efficacy in psoriasis treatment [178–181]. IL-6 and transforming growth factor β (TGF-β) released by dermal DCs elicit Retinoic Acid Receptor-Related Orphan Receptor Gamma-t (RORγt)-dependent differentiation of naive T cells into $T_{h/c}17$ cells [182–185]. IL-23 sustains the phenotype and expansion of $T_{h/c}17$ cells [186]. Psoriasis susceptibility is associated with SNPs in both subunits of IL-23, *IL12Bp40* and *IL23Ap19*, in *IL23R* [124,187,188], *TYK2* [126], *JAK2* [125] and *STAT3* [89] (Table 1). The IL-23 receptor is a heterodimer composed of IL-12Rβ1 and IL-23R [189]. A prominent coding SNP in *IL23R* reduces IL-23 signalling and is protective against psoriasis and other autoimmune diseases [190]. IL-23R associates with Jak2 and STAT3 while IL-12Rβ1 interacts directly with Tyk2 [189]. Proteins encoded by *TYK2*, *STAT3*, *SOCS1*, and *ETS1* are involved in downstream signalling of IL-23 [191,192]. IL-23 induced activation of STAT3 induces transcription of IL-17A and IL-17F [193]. STAT3 up-regulates the expression of the Th17-specific transcriptional regulator RORγt. A SNP within the gene for TRAF3 interacting protein 2 (*TRAF3IP2*) may influence NF-κB activation downstream of IL-17 receptor signalling and promote IL-17 induced effects [121,194,195]. Other genes (*ZC3H12C*, *IL12B*, *STAT5A*/*5B*, *ILF3*) refer to Th1 signalling pathways and interleukin 2 expression [132].

## 7. The pathogenetic cascade of HLA-associated IMDs

Together these insights propose an HLA-centered pathogenetic model for psoriasis and other HLA-associated IMDs. In this model a particular HLA allele represents the causal risk gene. It constitutes the essential disease prerequisite because it predisposes for a tissue- and antigen-specific autoimmune response through its capacity for autoantigen presentation. The HLA allele alone, however, is not sufficient for disease manifestation but requires the additive effects of common gene variants, which provide the functional environment for manifestation and differentiation of the actual autoimmune response.

From the perspective of the HLA-C*06:02-restricted T-cell mediated autoimmune response as central event in psoriasis pathogenesis, the pathogenic cascade can be differentiated into a proximal afferent and distal efferent phase (Fig. 1). In the upstream phase gene variants related to type-I IFN signalling and NF-κB activation may potentiate the innate immune response to trivial environmental triggers. This may promote the recruitment of inflammatory cells and production of proinflammatory mediators and chemokines, providing ample secondary signals for the HLA-restricted activation of potentially autoreactive non-cytotoxic $CD8^+$ T cells that may have been conditioned by certain gene variants during thymic $CD8^+$ T cell development and recognize peptides generated under the influence of certain ERAP1 variants. The efferent downstream phase involves gene variants related to the IL-23/IL-17 axis. They act on the maturation and differentiation of autoreactive $CD8^+$ T cells into a $T_c17$ phenotype, which is maintained by IL-23. Together with enhanced IL-17 signalling, the $T_c17$ cytokine pattern promotes keratinocyte hyperplasia, inflammation and recruitment of inflammatory cells. In this pathogenetic cascade the combination of particular risk gene activities may determine disease manifestation and phenotype in a polygenic manner [12]. In a case-case study *HLA-C*06:02* associated equally strong with mild and severe psoriasis. Strong additive effects for severe disease were observed when *HLA-C*06:02* combined with gene variants of *IL23A*, *IL23R*, *IL12B*, *NFKB1* or *TNIP1*. Thus, *HLA-C*06:02* confers an overall risk for psoriasis, while gene variants related to innate immune activation and the IL-23/T17 axis may modify disease expression [196].

## 8. Conclusion

Psoriasis is the first major IMD where the pathogenic role of the main HLA-risk gene could be unequivocally identified through the unbiased analysis of a pathogenic TCR. The HLA-C*06:02-restricted autoreactivity of the Vα3S1/Vβ13S1-TCR obtained directly from tissue-infiltrating psoriatic T cells provided direct evidence that disease-associated HLA-alleles can confer autoimmune susceptibility by facilitating tissue-specific autoimmune responses through presentation of particular autoantigens. These insights propose a concept for complex HLA-associated immune mediated disorders, where the genetic predisposition of IMDs combines a causative HLA-risk allele with the additive effects of many modifier genes that finally facilitate disease manifestation and modulate disease phenotype. This model attributes much of the missing heritability of IMDs to disease-associated HLA alleles, and it may inspire attempts to identify the missing autoantigens using similar approaches in other IMDs as well. This may finally allow for the development of biomarkers and novel causal therapies.

### Take-home messages

- The association of IMDs with particular HLA-alleles may reflect the capacity of the encoded HLA proteins to present self-peptides and induce an autoimmune response.
- Clonal T-cell expansions within the inflammatory tissue infiltrate of IMDs may reflect the activation and expansion of pathogenic T cells through stimulation by local tissue antigens.
- Because HLA-class I-molecules present antigens from cytoplasmic proteins, an HLA-class I restricted autoimmune response should naturally be directed against a particular target cell type.
- The particular target cell type may define the organ or tissue which is affected by the HLA-restricted autoimmune response.
- Identification of the autoimmune target cell type may be a prerequisite to identify and validate potential autoantigens, because the immunogenicity of particular self-proteins may be cell-type dependent.
- Because of TCR polyspecificity and cell-type specific differences in antigen processing, for a precise identification of disease-relevant HLA-class I-presented autoantigens it is not sufficient to determine peptide ligands for select TCRs but necessary to prove the immunogenicity of the peptide in the context of the parent protein within the target cell.
- The number of autoantigens relevant for an autoimmune disease is probably much smaller than the broad TCR reactivity against various natural peptide ligands would predict.
- HLA-alleles may account for the missing heritability of IMDs and facilitate the identification of autoimmune target cells and autoantigens.

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